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Impact of Body Mass Index on Outcomes in the Edoxaban Versus Warfarin Therapy Groups in Patients Undergoing Cardioversion of Atrial Fibrillation (From ENSURE-AF)

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Running Head: BMI, stroke and bleeding during cardioversion

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ABSTRACT

In the EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation (ENSURE-AF) study (NCT 02072434), edoxaban showed similar efficacy and safety vs enoxaparin–warfarin in patients undergoing electrical cardioversion of nonvalvular atrial fibrillation. In this ancillary analysis, we compared the primary efficacy (composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular [CV] death, overall study period) and safety (composite of major and clinically relevant nonmajor [CRNM] bleeding, on-treatment) endpoints in relation to body mass index (BMI; <30 vs ≥30 kg/m^2). We also compared cardioversion outcomes in relation to BMI. Of 2199 patients enrolled, 1095 were randomized to edoxaban and 1104 to enoxaparin–warfarin. Mean age was 64±10 and 64±11 years and mean BMI 30.6 and 30.7 kg/m^2, respectively. CV and metabolic diseases were more prevalent in obese (n = 1067) than nonobese patients. Overall ischemic event rates were low; rates in the BMI <30 kg/m^2 subgroup were numerically lower than the ≥30 kg/m^2 subgroup, but not significantly different (odds ratio [OR], 0.74 [95% confidence interval (CI) 0.23, 2.24]). Composite major + CRNM bleeding rates were low and numerically lower, but not significantly different (OR 0.88 [0.38,2.04]), between the edoxaban and enoxaparin–warfarin arms and across weight categories. Successful cardioversion rate was higher in the BMI <30 vs ≥30 kg/m^2 subgroup (73.9% vs 69.9%; OR 1.22 [1.01-1.48]). In ENSURE-AF, BMI did not significantly impact the relative efficacy and safety of edoxaban vs enoxaparin–warfarin. Nevertheless, the nonobese group had a higher rate of cardioversion success than the obese group.

Key Words: Body mass index, cardioversion, edoxaban, obesity

Introduction

Obesity is a risk factor for all-cause and cardiovascular (CV) death in the general population; however, an inverse relationship between being overweight or obese and a better CV prognosis is observed, the so-called "obesity paradox."[1-4] Our recent systematic review was suggestive of an obesity paradox in patients with atrial fibrillation (AF), particularly for all-cause and CV death outcomes.[3] In the nonvitamin K antagonist oral anticoagulant (NOAC) trials of stroke prevention in AF, an obesity paradox was also evident, with a treatment effect favoring NOACs over warfarin for both efficacy and safety that was significant only for normal-weight patients.[3,5] Nevertheless, there is uncertainty whether this obesity paradox is also evident for AF patients undergoing rhythm control. Certainly, weight reduction is associated with better outcomes following rhythm control,[6,7] but limited prospective trial data are available. In the Edoxaban Versus Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation (ENSURE-AF) trial, there were comparable low rates of major and clinically relevant nonmajor (CRNM) bleeding and thromboembolism when the oral factor Xa inhibitor edoxaban was compared with enoxaparin–warfarin.[8] This ancillary analysis from the ENSURE-AF trial compared clinical outcomes by body mass index (BMI, <30 vs ≥30 kg/m^2).

Methods

The design and principal results of the ENSURE-AF trial (NCT 02072434) have been published.[8,9] In brief, this was a multicenter, prospective, randomized, open, blinded endpoint trial in patients with nonvalvular AF undergoing electrical cardioversion that compared edoxaban 60 mg once daily with enoxaparin–warfarin in 2199 patients. Patients with an international normalized ratio (INR) <2.0 at randomization received enoxaparin bridging and daily warfarin until the INR was ≥2.0. Those with INR ≥2.0 at the time of randomization did not require enoxaparin and were treated with warfarin alone; hence, edoxaban was compared with "optimized anticoagulation" with enoxaparin–warfarin.

The primary efficacy endpoint was the composite of stroke, systemic embolic event (SEE), myocardial infarction (MI), and CV death during the overall treatment period from randomization until end of study and the primary safety endpoint was the composite of major and CRNM bleeding during the on-treatment period (time of first dose to last dose of study drug taken). Successful cardioversion was confirmed by 12-lead electrocardiogram-documented sinus rhythm. The trial protocol was approved by ethics committees or institutional review boards. All patients provided written informed consent prior to participation in the study. This ancillary analysis compared the primary efficacy and safety endpoints with clinical outcomes by BMI (<30 vs ≥30 kg/m^2).

Patients were followed for 28 days on study drug after cardioversion plus another 30 days to assess safety, which were analyzed in relation to body weight and BMI. For enoxaparin–warfarin patients, the clinical characteristics were summarized by BMIs of <30 and ≥30 kg/m^2, with categorical variables as frequencies and percentages, and continuous variables as mean and standard deviation. Comparison of clinical characteristics for patients with BMI <30 and ≥30 kg/m^2 using the chi-square test for categorical variables and 1-way analysis of variance for continuous variables were provided.

The number and percent of patients with primary efficacy and safety outcomes were provided by treatment arm. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented to assess the difference between treatment arms. We also explored outcomes in relation to BMI as a continuous variable. In addition, successful cardioversion in patients with BMI <30 kg/m^2 were compared with those with BMI ≥30 kg/m^2. The number and percent of patients with successful cardioversion were provided by BMI category. Odds ratios and 95% CIs are presented to assess the difference between BMI categories.

Results

Of 2199 patients enrolled, 1095 were randomized to edoxaban and 1104 to enoxaparin–warfarin. Mean ± standard deviation (SD) age was 64.3 ± 10 and 64.2 ± 11 years and mean BMI 30.6 and 30.7 kg/m^2, respectively. In all, 1067 patients had a BMI of ≥30 kg/m^2; among these obese patients, CV and metabolic diseases were more prevalent than in nonobese patients, as confirmed by the use of statins and antihypertension medications (**Table 1**). Mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [2 points], diabetes mellitus, stroke [2 points], vascular disease, age 65–74 years, sex category) and HAS-BLED (hypertension, age, stroke, bleeding tendency/predisposition, labile INRs, elderly age/frailty, drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs or alcohol excess) scores were significantly higher in the obese subgroup, suggesting they were at greater risk for stroke and bleeding. There were no relevant differences in time to therapeutic range and time in therapeutic range in relation to BMI <30 vs ≥30 kg/m^2.

Rates of composite stroke/SEE, MI or CV mortality rates were low and numerically lower for obese patients relative to nonobsee patients, but were nonsignificant (OR 0.74 [0.23, 2.24]) even for both the edoxaban and enoxaparin–warfarin arms and across weight categories.

Composite major and CRNM bleeding rates were low and numerically lower for obese patients relative to nonobsese patients (OR 0.88 [0.38, 2.04]), as well as being nonsignificant in both the edoxaban and enoxaparin–warfarin arms and across weight categories. Major bleeding rates were numerically lower, but nonsignificant across weight categories (OR 0.32 [0.0, 1.8]).

Successful cardioversion was significantly more likely in those with BMI <30 kg/m^2 (OR 1.22 [1.01–1.48]) (**Table 2**). Mean BMI was slightly lower in those with successful cardioversion compared to those with unsuccessful cardioversion (30.56 (SD 5.71) vs 31.22 (5.45; p=0.0472).

In a logistic regression analysis with the composite of major and CRNM bleeding as the response variable; and treatment, numerical BMI, and their interaction as independent variables; the p-values for treatment, BMI, and interaction were 0.8852, 0.9016, and 0.9662, respectively (data not shown).

When comparing BMI <30 vs ≥30 kg/m^2, composite ischemic events (stroke/SEE, MI, and CV mortality) were numerically lower, but given the low overall rates, this was nonsignificant (on-treatment analysis OR 0.74 [95% CI 0.23, 2.24]). In a logistic regression analysis with primary efficacy endpoint as the response variable; and treatment, numerical BMI, and their interaction as independent variables; the p-values for treatment, BMI, and interaction were 0.0645, 0.2022 and 0.1034, respectively (data not shown).

Outcomes in relation to BMI as a continuous variable are shown in **Figure 1**. For major plus CRNM bleeding (on-treatment analysis), no relationship was apparent between BMI and treatment with edoxaban or enoxaparin–warfarin. For stroke/SEE, MI and CV mortality, there was a trend toward lower event rates with increasing BMI in the enoxaparin–warfarin group. For edoxaban, few events were seen at lower BMI values to show any trends, but no difference was observed when compared with enoxaparin–warfarin at higher BMI values. The proportion with successful cardioversion was higher in the BMI <30 kg/m^2 subgroup (827/1119; 73.9%) compared with the BMI ≥30 kg/m^2 subgroup (745/1067; 69.9%) (OR 1.22 [1.01–1.18]), p = 0.038. In a logistic regression analysis with successful cardioversion as the response variable; and treatment, numerical BMI, and their interaction as independent variables; the p-values for treatment, BMI, and interaction are 0.7168, 0.2265, and 0.6644, respectively.

Discussion

In this ancillary analysis from ENSURE-AF, the data suggests that obesity does not influence the rate of ischemic events after cardioversion regardless of the therapeutic strategy. The BMI <30 kg/m^2 group had a higher rate of cardioversion success than the BMI ≥30 kg/m^2 group; and edoxaban had comparable efficacy and safety to optimized usual anticoagulation with enoxaparin–warfarin, and were not significantly different in various BMI categories.

Our systematic review found that only obese patients were at lower risk for major bleeding compared with normal-weight patients.[3] In the present analysis from ENSURE-AF, no significant relationship was evident between the primary bleeding outcome and BMI. The present patient population was at low bleeding risk, as evident by a mean HAS-BLED score of 0.9. While guidelines advocate focus on modifiable bleeding risk factors, recent evidence shows that the HAS-BLED score is a better assessment of the AF patient's potential bleeding risk compared with simply using modifiable bleeding risk factors.[10-12]

In a prior systematic review and metaanalysis, we found that there may be an obesity paradox in AF patients for all-cause and cardiovascular death outcomes.[3] An obesity paradox was also seen for stroke/SEEs, with a treatment effect favoring NOACs over warfarin for both efficacy and safety that was significant only for normal-weight patients. In the present analysis from ENSURE-AF, obesity did not influence the rate of the composite efficacy events (stroke/SEE, MI, and CV mortality) after cardioversion regardless of treatment with NOAC or enoxaparin–warfarin. This is despite the ENSURE-AF trial including a relatively high-risk patient population for stroke (mean CHA_2DS_2VASc score 2.6), that was broadly comparable to the patient population in the ENGAGE-AF trial[13] (mean $CHADS_2$ score 2.8) and other NOAC stroke prevention trials.[14] Nonetheless, the followup duration in ENSURE-AF was shorter than that in the ENGAGE-AF trial.

As expected from prior studies,[15,16] cardioversion success was lower in obese patients. This may reflect associated comorbidities or a greater body impedance relevant to ENSURE-AF since electrical cardioversion was the only modality used. Indeed, pharmacological cardioversion is perhaps more advocated in obese subjects with AF.

Although the ENSURE-AF trial is the largest study in AF pericardioversion to date, this study is limited by being a subgroup analysis of a selected clinical trial cohort, and the results may not be applicable to the general AF population. BMI measurement and categorization of obesity was based on baseline measures, and changes in BMI over time were not considered. Also, the low overall event rates and short follow-up period may have influenced outcome event rates, which may be underpowered.

In conclusion, edoxaban had efficacy and safety comparable with optimized standard anticoagulation with enoxaparin-warfarin; neither treatment group showed significant differences in various BMI categories. Obesity did not influence the rate of ischemic events after cardioversion regardless of the therapeutic strategy. Nevertheless, the BMI <30 kg/m^2 group had a higher rate of cardioversion success than the obese group.

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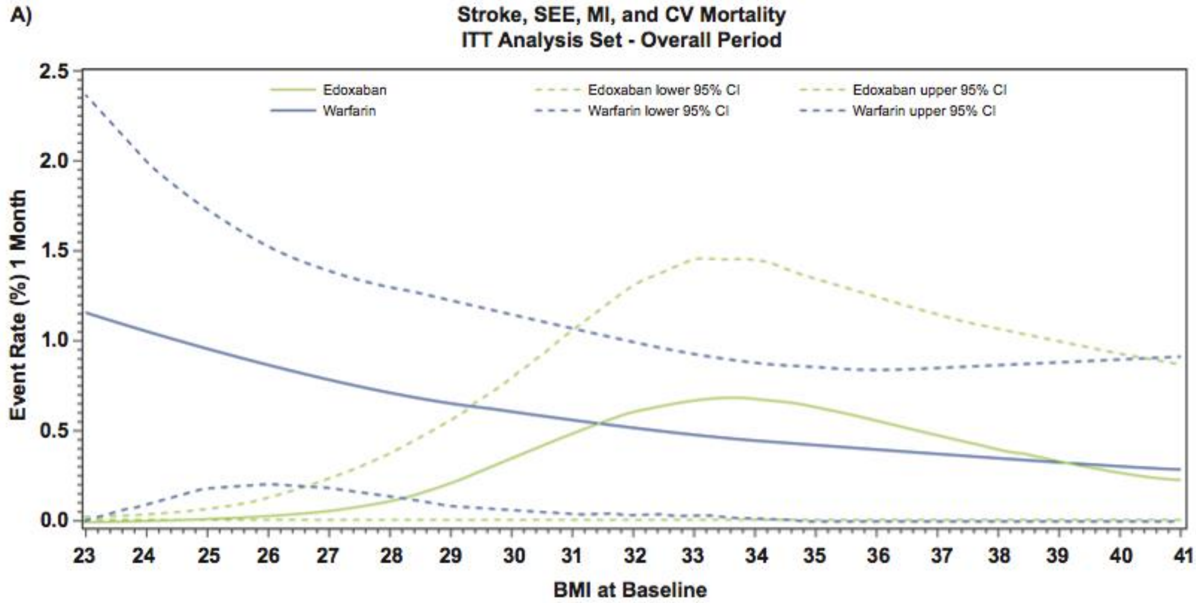
Figure Legend

A)



BMI, body mass index; CI, confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; MI, myocardial infarction; SEE, systemic embolic event.

B)

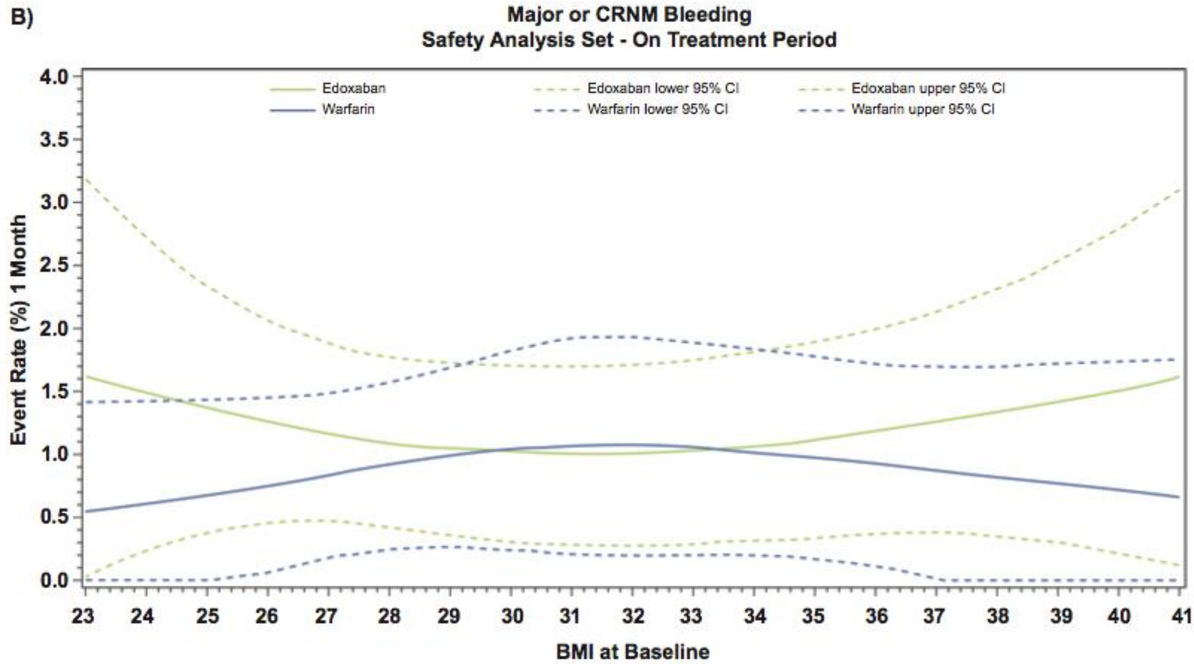


Figure 1. Event rate at one month of primary efficacy outcomes and BMI for A) Stroke, SEE, MI, and CV and B) major or CRNM bleeding . a) Stroke, SEE, MI, and CV Mortality, ITT Analysis Set - Overall Period; b) Stroke, SEE, MI, and CV Mortality, Safety Analysis Set - On Treatment Period.

Table 1. Baseline Characteristics by BMI

			BMI (kg/m^2)						
	Overall		<30			≥30			
Variable	**Edoxaban (N = 1095)**	**Enoxaparin–warfarin (N = 1104)**	**Edoxaban (n = 560)**	**Enoxaparin–warfarin (n = 559)**	**Total (n = 1119)**	**Edoxaban (n = 530)**	**Enoxaparin–warfarin (n = 537)**	**Total (n = 1067)**	**p-value†**
Age, mean, SD	64.3 (10.3)	64.2 (10.8)	65.6 (11.1)	65.1 (11.3)	65.4 (11.2)	62.9 (9.3)	63.2 (10.1)	63.0 (9.7)	<0.0001
>65	509 (46.5%)	530 (48.0%)	293 (52.3%)	287 (51.3%)	580 (51.8%)	212 (40.0%)	239 (44.5%)	451 (42.3%)	
Weight, kg, mean (SD)	90.9 (18.3)	91.2 (19.0)	79.4 (11.3)	78.8 (11.4)	79.1 (11.3)	102.9 (16.5)	104.1 (16.6)	103.5 (16.6)	<0.0001
≤60	21 (1.9%)	33 (3.0%)	21 (3.8%)	33 (5.9%)	54 (4.8%)	0	0	0	
Anticoagulant experienced, n (%)									
Current* VKA user	513 (46.8)	558 (50.5)	257 (45.9)	298 (53.3)	555 (49.6)	254 (47.9)	259 (48.2)	513 (48.1)	0.4935
Current* NOAC user	157 (14.3)	148 (13.4)	78 (13.9)	70 (12.5)	148 (13.2)	77 (14.5)	78 (14.5)	155 (14.5)	0.3866
CrCl, mean (SD)	94.0 (35.7)	94.1 (34.7)	81.2 (29.2)	81.1 (27.9)	81.2 (28.6)	107.5 (37.1)	108.0 (35.9)	107.7 (36.5)	<0.0001
TtTR (days), mean (SD)	-	7.7 (5.1)	-	7.4 (4.9)	-	-	7.9 (5.4)	-	0.2428
TiTR (% of time), mean (SD)	-	70.8 (27.4)	-	72.0 (26.9)	-	-	69.8 (28.0)	-	0.2153
TTR (% of time), mean (SD)	-	59.8 (30.6)	-	60.5 (30.1)	-	-	59.3 (31.1)	-	0.5646
Heart Failure	476 (43.5%)	484 (43.8%)	219 (39.1%)	239 (42.8%)	458 (40.9%)	256 (48.3%)	245 (45.6%)	501 (47.0%)	0.0051
Coronary Artery Disease	181 (16.5%)	197 (17.8%)	79 (14.1%)	93 (16.6%)	172 (15.4%)	102 (19.2%)	104 (19.4%)	206 (19.3%)	0.0174
Hypertension	850 (77.6%)	864 (78.3%)	399 (71.3%)	397 (71.0%)	796 (71.1%)	448 (84.5%)	464 (86.4%)	912 (85.5%)	<0.0001
Diabetes	218 (19.9%)	197 (17.8%)	80 (14.3%)	57 (10.2%)	137 (12.2%)	137 (25.8%)	139 (25.9%)	276 (25.9%)	<0.0001
Peripheral Artery Disease	40 (3.7%)	54 (4.9%)	25 (4.5%)	30 (5.4%)	55 (4.9%)	15 (2.8%)	24 (4.5%)	39 (3.7%)	0.1702
Valvular Heart Disease	250 (22.8%)	240 (21.7%)	133 (23.8%)	140 (25.0%)	273 (24.4%)	116 (21.9%)	100 (18.6%)	216 (20.2%)	0.0209
Intracranial Haemorrhage	2 (0.2%)	3 (0.3%)	0	1 (0.2%)	1 (0.1%)	2 (0.4%)	2 (0.4%)	4 (0.4%)	0.2077
Ischemic stroke/Transient Ischaemic Attack	68 (6.2%)	66 (6.0%)	41 (7.3%)	39 (7.0%)	80 (7.1%)	26 (4.9%)	27 (5.0%)	53 (5.0%)	0.0392
Myocardial Infarction	69 (6.3%)	78 (7.1%)	37 (6.6%)	37 (6.6%)	74 (6.6%)	32 (6.0%)	41 (7.6%)	73 (6.8%)	0.8645
Life-threatening bleed	3 (0.3%)	3 (0.3%)	1 (0.2%)	1 (0.2%)	2 (<0.1%)	2 (0.4%)	2 (0.4%)	4 (0.4%)	0.4421
AF history									
Paroxysmal (≤7 days)	208 (19.0%)	207 (18.8%)	105 (18.8%)	115 (20.6%)	220 (19.7%)	103 (19.4%)	92 (17.2%)	195 (18.3%)	0.4450
Persistent (>7 days, <1 yr)	887 (81.0%)	890 (80.6%)	455 (81.3%)	444 (79.4%)	899 (80.3%)	427 (80.6%)	443 (82.8%)	870 (81.5%)	0.4450
CHA_2DS_2-VASc score, mean (SD)	2.6 (1.5)	2.6 (1.4)	2.6 (1.6)	2.5 (1.4)	2.5 (1.50)	2.7 (1.4)	2.7 (1.4)	2.7 (1.4)	0.0101
HAS-BLED Score, mean (SD)	0.9 (0.8)	0.9 (0.8)	0.9 (0.8)	0.9 (0.8)	0.9 (0.78)	0.8 (0.8)	0.9 (0.8)	0.9 (0.8)	0.0361
Drug therapies									
Aspirin	192 (17.5%)	221 (20.0%)	100 (17.9%)	105 (18.8%)	205 (18.3%)	92 (17.4%)	114 (21.2%)	206 (19.3%)	0.5841
Statins	429 (39.2%)	411 (37.2%)	211 (37.7%)	188 (33.6%)	399 (35.7%)	216 (40.8%)	220 (41.0%)	436 (40.9%)	0.0136
ACEI/ARB	692 (63.2%)	688 (62.3%)	322 (57.5%)	308 (55.1%)	630 (56.3%)	368 (69.4%)	376 (70.0%)	644 (60.4%)	<0.00010.
Beta blockers	862 (78.7%)	847 (76.7%)	425 (75.9%)	434 (77.6%)	859 (76.8%)	434 (81.9%)	410 (76.4%)	844 (79.1%)	1975

*Current defined as using VKA or NOAC at randomization or within 30 days prior to randomization. Percentages are based on the numbers of anticoagulant experienced.

†Comparisons between total columns for BMI <30 and BMI ≥30.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, stroke (2 points), vascular disease, age 65–74 years, sex category; CrCl, creatinine clearance; HAS-BLED, hypertension, age, stroke, bleeding tendency/predisposition, labile INRs, elderly age/frailty, drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs or alcohol excess; HF, heart failure; ICH, intracerebral hemorrhage; MI, myocardial infarction; NOAC, nonvitamin K antagonist oral anticoagulant; PAD, peripheral arterial disease; SD, standard deviation; VHD, valvular heart disease; TIA, transient ischemic stroke; TiTR, time in therapeutic range (calculated from the first day with 2≤ INR ≤3); TTR, time in therapeutic range (calculated from day 8 of study drug); TtTR, time to achieve therapeutic range; VKA, vitamin K antagonist.

Table 2. Event Rates by BMI

	Overall		BMI <30 kg/m^2		BMI ≥30 kg/m^2	
	Edoxaban	Enoxaparin–Warfarin	Edoxaban	Enoxaparin–Warfarin	Edoxaban	Enoxaparin–Warfarin
First stroke, SEE, MI, or CV mortality[*]						
N	1095	1104	560	559	530	537
n (%)	5 (0.5%)	11 (1.0%)	1 (0.2%)	6 (1.1%)	4 (0.8%)	5 (0.9%)
OR (95% CI)	0.46 (0.12, 1.43)		0.17 (0, 1.37)		0.81 (0.16, 3.78)	
Major or CRNM bleeding events[†]						
N	1067	1082	547	551	517	528
n (%)	16 (1.5%)	11 (1.0%)	8 (1.5%)	5 (0.9%)	8 (1.6%)	6 (1.1%)
OR (95% CI)	1.48 (0.64, 3.55)		1.62 (0.46, 6.34)		1.37 (0.41, 4.82)	
Major bleeding events[†]						
N	1067	1082	547	551	517	528
N (%)	3 (0.3%)	5 (0.5%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	4 (0.8%)
OR (95% CI)	0.61 (0.09, 3.13)		1.01 (0.01, 79.21)		0.51 (0.05, 3.57)	
Successful cardioversion						
N	1095[‡]	1104[§]	560	559	530	537
n (%)	790 (72.2%)	788 (71.4%)	414 (73.9%)	413 (73.9%)	374 (70.6%)	372 (69.3%)
OR (95% CI)	1.04 (0.86, 1.26)		1.00 (0.76, 1.32)		1.06 (0.81, 1.39)	

	BMI <30 kg/m^2	BMI ≥30 kg/m^2
First stroke, SEE, MI, or CV mortality[*]		
N	1119	1067
n (%)	7 (0.6%)	9 (0.8%)
OR (95% CI)	0.74 (0.23, 2.24)	
Major or CRNM bleeding events[†]		
N		
n (%)	1098	1045
OR (95% CI)	13 (1.2%)	14 (1.3%)
	0.88 (0.38, 2.04)	
Major bleeding events[†]		
N	1098	1045
n (%)	2 (0.2%)	6 (0.6%)
OR (95% CI)	0.32 (0.0, 1.8)	
Successful cardioversion[‡]		
N	1119	1067
n (%)	827 (73.9%)	746 (69.9%)

OR (95% CI)	1.22 (1.01, 1.48)

[*]ITT population, overall study period (28 days on study drug after cardioversion + 30 days follow-up).

[†]All treated patients, on-treatment period (time of first dose to last dose of study drug taken).

BMI, body mass index; CI, confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; ITT, intention to treat; MI, myocardial infarction; OR, odds ratio; SEE, systemic embolic event.

[‡]Data for BMI was not available for 5 patients.

[§]Data for BMI was not available for 8 patients.